REMARKS

Applicant respectfully requests reconsideration. Claims 100-102 and 105-118 were previously pending in this application. By this amendment, Applicant is canceling claims 114-118 without prejudice or disclaimer. Claims 108 has been amended for clarification purposes. No new claims have been added. Claims 100-102 and 105-107 are allowed. As a result, claims 100-102 and 105-113 are pending for examination with claims 100 and 108 being independent claims. No new matter has been added.

Allowable Subject Matter

Applicant acknowledges that claims 100-102 and 105-107 are allowed.

Election Restriction

According to the Office, claims 115-118 are directed to a species that was not elected. Further, according to the Office, in the election restriction of August 2, 2006, Applicant elected SEQ ID NO:313, and claims 115-118 are therefore withdrawn.

Applicant respectfully disagrees with the statement by the Office that claims 115-118 were not elected. In the response submitted July 28, 2006, Applicant elected Group I, which includes the then pending claims 66, 67, 97 and 98 (corresponding to currently pending claims 115-118). However, in the interest of expediting prosecution, Applicant has canceled claims 115-118.

Rejections Withdrawn

Applicant acknowledges the withdrawal by the Office of the rejection of claims 100-102 and 104-107 under 35 USC §103(a).

Double Patenting Rejection

The Office provisionally rejected claim 108 on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claim 20 of U.S. application No. 11/361,313.

Applicant submits that a terminal disclaimer over U.S. Serial No. 11/361,313 may be provided, if appropriate, upon a determination of allowable subject matter.

Rejections under 35 U.S.C. §112

The Office rejected claim 114 under 35 U.S.C. §112 as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Applicant respectfully disagrees with the assertion by the Office. However, in the interest of expediting prosecution, Applicant has canceled claim 114. Applicant believes the rejection is moot therefore.

Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

Rejections Under 35 U.S.C. §103

The Office rejected claims 108-114 under 35 U.S.C. §103(a) as allegedly being unpatentable over Krieg et al. (WO01/22972), as evidenced by Yamamoto et al. (1994, Microbiol. Immunol. 38: 831-836). According to the Office, Krieg et al. teaches the sequence 343, which correlates to an immunostimulatory nucleic acid having at least one internal cytosine-guanine dinucleotide wherein optionally each internal YZ dinucleotide is a stabilized internucleotide linkage. According to the Office, "it would have been *prima facie* obvious to incorporate a phosphodiester internucleotide linkage as taught by Krieg et al. in the CG dinucleotide...in order to take advantage of using vehicles to improve cell uptake in order to enhance the immune stimulatory effects". In addition, according to the Office, "it would have been equally obvious to at the time the invention was made to incorporate phosphodiester internucleotide linkage in the CG dinucleotide with a chimeric

backbone in order to take advantage of modified nucleic acids that show more stimulatory activity due to enhanced nuclease resistance and increased cellular uptake, increased protein binding".

Applicant respectfully traverses. Krieg et al., as evidenced by Yamamoto et al., does not render obvious the claimed oligonucleotides at least because the claimed oligonucleotides provide an unexpected result over the art of record.

In the previous response Applicant demonstrated that oligonucleotides having SEQ ID NO:313 show an unexpected result over the art of record. Namely, it was unexpected that replacing a stabilized internucleotide linkage with a non-stabilized linkage within a cytosine-guanine dinucleotide would result in an oligonucleotide with similar or improved immunostimulatory properties. The Office has since withdrawn the obviousness rejection and has indicated that the claims reciting oligonucleotides having SEQ ID NO:313 are free of the art of record.

Applicant submits that the genus of oligonucleotides of the currently rejected claims show the same unexpected properties as the encompassed species of oligonucleotides having SEQ ID NO:313 and that the oligonucleotides of the rejected claims were therefore non-obvious over the art of record.

The properties of the claimed oligonucleotides were unexpected at the time of the effective filing date of the instant application. It is shown in the instant application that replacing a stabilized phosphorothioate internucleotide linkage with a non-stabilized phosphodiester linkage within a pyrimidine-purine dinucleotide in a fully stabilized oligonucleotide (having only phosphorothioate linkages) provides oligonucleotides with similar or improved immunostimulatory properties as compared to the fully stabilized oligonucleotide. As shown in the previous response this was unexpected based on the teachings in the art at the time of the effective filing date of the application. At the time of filing the art taught that oligonucleotides with stabilized internucleotide linkages have increased immunostimulatory activity as compared to oligonucleotides without stabilized internucleotide linkages. Based on the art at the time of filing, a person of ordinary skill in the art

would have expected that replacing a stabilized internucleotide linkage (*e.g.,* a phosphorothioate linkage) with a non-stabilized linkage (*e.g.,* a phosphodiester linkage) would result in an oligonucleotide that would be prone to intracellular cleavage at the phosphodiester linkage, and therefore more susceptible to degradation *in vivo*. In particular, the skilled artisan would not have placed the phosphodiester linkage within the critical immunostimulatory motif (*e.g.,* between the C and G in the CpG motif) because of the expectation that the oligonucleotide would become more susceptible to cleavage within the critical motif and break into shorter oligonucleotides that do not include the critical motif. Thus, in the absence of the findings of the invention, it was expected that placing the phosphodiester linkage within the critical immunostimulatory motif would decrease the immunostimulatory activity of an oligonucleotide.

The expectation in the art at the time of filing of the application that the claimed oligonucleotides would have decreased immunostimulatory properties is exemplified by the references discussed in the previous response (Krieg et al., Hartmann et al., Parronchi et al., and Samani et al.). The references all demonstrate that at the time of filing of the application, a person of ordinary skill in the art would have expected that replacing a stabilized internucleotide linkage (*e.g.,* a phosphorothioate linkage) with a non-stabilized linkage (*e.g.,* a phosphodiester linkage) would decrease the activity of the oligonucleotide.

Applicant submits herewith a declaration by Dr. Arthur Krieg, an expert in the fields of immunology and immunostimulatory oligonucleotides. Dr. Krieg is both the first named inventor of the instant application and the first named inventor of the cited art reference Krieg et al. (WO01/22972). Dr. Krieg states that at the time of filing a person of ordinary skill in the art would have expected that CpG oligonucleotides having stabilized internucleotide linkages would have some increased activity, for instance B cell activity, as compared to CpG oligonucleotides without stabilized internucleotide linkages, and that replacing the stabilized internucleotide linkage with a non-stabilized linkage within a CpG dinucleotide, while adjacent non-CpG dinucleotides linkages remain stabilized, would have been expected to result in an oligonucleotide with decreased immunostimulatory activity. Thus, the declaration by Dr. Krieg establishes that the findings of the

instant application were unexpected because at the time of filing of the application a person of ordinary skill in the art would have expected that the claimed oligonucleotides would have decreased immunostimulatory activity compared to fully stabilized versions of the same oligonucleotides.

The specification supports that the unexpected result is found for the whole breadth of the claimed genus of oligonucleotides. Replacing at least one stabilized internucleotide linkage with a non-stabilized linkage within a cytosine-guanine dinucleotide in a fully stabilized oligonucleotide will result in an oligonucleotide with similar or improved immunostimulatory properties, regardless of the specific composition of the oligonucleotide.

In the declaration submitted herewith, Dr. Krieg states that the data in the application show that the unexpected high immunostimulatory activity is achieved for a broad spectrum of oligonucleotides having a non-stabilized linkage within a cytosine-guanine dinucleotide. Dr. Krieg refers to the data Table 6 (pages 93-94) of the application which shows that oligonucleotides having different sequences, different lengths, or different numbers of pyrimidine-purine dinucleotides all show similar or increased immunostimulatory activity when a stabilized linkage within a pyrimidine-purine dinucleotide is replaced with a non-stabilized linkage.

Table 6 provides that, regardless of the sequence composition of the fully stabilized oligonucleotide, replacing a phosphorothioate internucleotide linkage with a phosphodiester linkage within one or more cytosine-guanine dinucleotides results in improved immunostimulatory properties. Compare for instance oligonucleotides with SEQ ID NO: 256 and SEQ ID NO: 282. Both oligonucleotides, even though they have different sequences, show improved immunostimulatory properties when a phosphorothioate linkage is replaced with a non-stabilized phosphodiester within a cytosine-guanine dinucleotide linkage.

Table 6 also provides that, regardless of the length of the fully stabilized oligonucleotide, replacing a phosphorothioate internucleotide linkage with a phosphodiester linkage within one or

more cytosine-guanine dinucleotides results in improved immunostimulatory properties. Compare for instance SEQ ID NO: 260 (a 24-mer oligonucleotide) and SEQ ID NO: 282 (an 18-mer oligonucleotide). Both oligonucleotides, even though they have different lengths, show improved immunostimulatory properties when a phosphorothioate linkage is replaced with a non-stabilized phosphodiester bond within a cytosine-guanine dinucleotide linkage.

Table 6 also provides that, regardless of the number of cytosine-guanine dinucleotide within an otherwise fully stabilized oligonucleotide, as long as at least one phosphorothioate internucleotide linkage is replaced, an oligonucleotides will have improved immunostimulatory properties. Compare for instance SEQ ID NO: 254 and SEQ ID NO: 256, which both show improved immunostimulatory properties, even though a different number of phosphorothioate linkages are replaced with non-stabilized phosphodiester linkages.

Table 6 also provides examples of oligonucleotides having a non-stabilized linkage within a cytosine-guanine dinucleotide that have an immunostimulatory activity that is similar to the fully stabilized version (See, *e.g.,* SEQ ID NO:251 and SEQ ID NO:267). It should be noted that the similar activity is still an unexpected result as a person of ordinary skill in the art would have expected that oligonucleotides having a non-stabilized linkage within a cytosine-guanine dinucleotide would have decreased immunostimulatory activity compared to fully stabilized versions of the same oligonucleotides.

The specification therefore provides support for unexpected results the full the breadth of the genus of claimed oligonucleotides.

In conclusion, Applicant has established, both through the declaration of Dr. Krieg, and by the showing in teachings in the art at the time of filing, that a person of ordinary skill in the art would have not expected that the claimed oligonucleotides would have the similar or increased immunostimulatory properties (compared to the fully stabilized versions). In addition, Applicant has established, both through the declaration of Dr. Krieg, and by the teachings of the specification,

that the unexpected results are found for the full breadth of the genus of claimed oligonucleotides. Thus, because the claimed oligonucleotides provide an unexpected result over the art of record, the claimed oligonucleotides were non-obvious over the art of record.

Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

A Notice of Allowance is respectfully requested. The Office is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, the Director is hereby authorized to charge any deficiency or credit any overpayment in the fees filed, asserted to be filed or which should have been filed herewith to our Deposit Account No. 23/2825, under Docket No.: C1037.70048US00.

Dated: February 3, 2011

Respectfully submitted,

By: /Erik J. Spek/
Erik J. Spek, Ph.D.,
Registration No.: 61,065
WOLF, GREENFIELD & SACKS, P.C.
Federal Reserve Plaza
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
617.646.8000